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Total Number of Pages in This Submission: 27

Application Number	09/844,544
Filing Date	April 27, 2001
First Named Inventor	ZENG, DEFU
Group Art Unit	1644
Examiner Name	DIBRINO, MARIANNE
Attorney Docket Number	STAN-190

ENCLOSURES (check all that apply)

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Signing Attorney/Agent (Reg. No.)	PAMELA J. SHERWOOD, 36,677 BOZICEVIC, FIELD & FRANCIS, LLP
Signature	Pamela Sherwood
Date	October 28, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

EXPRESS MAIL: EV519866175US OCT. 28, 2004

Attorney Docket	STAN-190
First Named Inventor	D. Zeng
Application Number	09/844,544
Filing Date	April 27, 2001
Group Art Unit	1644
Examiner Name	M. Dibrino
Title: *Methods for Inhibition of Polyclonal B Cell and Immunoglobulin Class Switching to Pathogenic Autoantibodies by Blocking CD1-Mediated Interactions*	

Commissioner for Patents
Alexandria, VA 22313

BRIEF ON APPEAL

REAL PARTY IN INTEREST

The real party in interest is The Board of Trustees of the Leland Stanford Junior University, to which all rights have been assigned, as evidenced by the assignment recorded on April 27, 2001, reel and frame 011771/0601.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

RELATED PATENTS AND APPLICATIONS

The present application claims benefit of priority to U.S. Provisional Application no. 60/200,285.

STATUS OF CLAIMS

The present application was filed on April 27, 2001 with original claims 1-14 pending. Following the Restriction Requirement of October 2, 2002, claims 3, 11 and 14 were withdrawn from consideration. In Applicants response of June 6, 2003, claims 4-5 and 9 were canceled. In Applicants response of December 19, 2003, claims 3, 11 and 14 were canceled. The presently pending claims are 1-2, 6-8, 10, 12 and 13.

STATUS OF AMENDMENTS

During prosecution of the present application, on June 6, 2003, a response to the Office Action dated February 12, 2003 was filed amending claims 1, 6, 8, 10 and 13 and canceling claims 4-5 and 9, which amendment was entered. On December 19, 2003, a response to the Final Office Action dated October 21, 2003 was filed, canceling claims 3, 11 and 14, and amending claim 1. The Advisory Action of April 8, 2004 stated that the Amendments would be entered for purposes of appeal.

SUMMARY OF THE INVENTION

Certain autoimmune diseases are the result of polyclonal stimulation of B cells and overproduction of antibodies, particularly autoantibodies of a pathogenic isotype. Systemic lupus erythematosus (SLE) is an example of an autoimmune disease characterized by polyclonal B cell activation, which results in a variety of anti-protein and non-protein autoantibodies. These autoantibodies form immune complexes that deposit in multiple organ systems, causing tissue damage. SLE is a difficult disease to study, having a variable disease course characterized by exacerbations and remissions. Disease manifestations result from recurrent vascular injury due to immune complex deposition, leukothrombosis, or thrombosis. Additionally, cytotoxic antibodies can mediate autoimmune hemolytic anemia and thrombocytopenia, while antibodies to specific cellular antigens can disrupt cellular function.

CD1 is a nonpolymorphic, class I MHC-like, non-MHC encoded molecule that may be found non-covalently associated with β_2-microglobulin (β_2m). CD1 molecules have been demonstrated to be antigen-presenting molecules for glycolipid and hydrophobic peptides. A natural ligand of murine CD1d has been reported to be glycosylphosphatidylinositol (GPI).

In the presently claimed methods, blocking antibodies, which specifically interact with CD1 antigen recognition, but do not activate signaling, are administered to a patient, and act to inhibit the function of T cells that recognize CD1. When CD1 mediated signaling is thus blocked, the T cell response is diminished, resulting in reduced polyclonal B cell activation and Ig class switching. Treatment with anti-CD1 monoclonal antibodies significantly delays the onset of proteinuria, reduces the levels of serum IgG and anti-dsDNA IgG and prolongs survival in a model system for SLE.

T cells that recognize peptides derived from nucleosomes or anti-DNA antibodies augment the secretion of pathogenic anti-DNA IgG antibodies in a model for SLE. However, it has not been

understood how conventional T cells recognizing peptides associated with MHC molecules can provide help for B cells secreting antibodies that are directed to non-protein antigens.

The present invention demonstrates that an interaction between CD1 expressing B cells and CD1 reactive T cells play an important role in the development of lupus, and that the progression of disease can be inhibited by the administration of blocking reagents that interfere with CD1 mediated signaling.

ISSUE ON APPEAL

Claims 1-2, 6-8, 10 and 12 have been rejected under 35 U.S.C. 103(a) as unpatentable over Amano *et al.* in view of Kotzin *et al.*, Zeng *et al.*, Blumberg *et al.* and Hughes.

Claim 13 has been rejected under 35 U.S.C. 103(a) as unpatentable over Amano *et al.* in view of Kotzin *et al.*, Zeng *et al.*, Blumberg *et al.* and Hughes, further in view of the Merck Manual.

GROUPING OF CLAIMS

For purposes of the rejection made under 35 U.S.C. 103, first paragraph, the claims stand or fall together.

ARGUMENTS

Appellants respectfully submit that the presently claimed invention is not made obvious by the cited prior art. The present claims are directed to a method of treatment for pathogenic polyclonal B cell activation or class switching in a patient by the administration of antibodies or fragments thereof that bind to CD1 and interfere with T cell recognition of CD1.

Key to the invention is the demonstration provided by Appellants that *in vivo* blocking of CD1 by administration of antibodies significantly reduced the peak levels of serum IgG and IgG anti-dsDNA autoantibodies, and delayed disease progression. Importantly, these results were obtained with a spontaneous disease model representative of clinical disease. The present invention is based on results that were unexpected in view of the cited art.

As will be shown below, the prior art teachings of the primary reference Amano *et al.* (and the work of Zeng *et al.*, which is cited by Amano *et al.*) relate to work with animals that were made to be transgenic for a T cell receptor that recognizes CD1. These transgenic animals do not develop any pathogenic polyclonal B cell activation. Specific subpopulations of transgenic T cells from these

animals can be transferred to cause disease, but at the same time, other populations of these transgenic T cells, which are more representative of native populations, suppress disease.

From the teachings of the prior art, one of skill in the art could not conclude with any degree of certainty that CD1 would have a causative effect in spontaneous lupus. Although the art suggested a possible connection between spontaneous lupus and CD1, there was substantial uncertainty that CD1 had a causative role, or was merely associated with the disease in these systems. Without the findings provided in the present application, one of skill in the art could not have a reasonable certainty of success practicing the claimed methods.

Indeed, in some instances prior art teaches away from the present invention. Prior to Applicants showing of the involvement of CD1 reactive cells (NKT cells), it was believed that the NKT cells were protective for lupus, not causative (see Takeda *et al.* (1993) J. Exp. Med. 177:155).

The Patent Office has cited Amano *et al.* as a primary reference. Amano *et al.* demonstrate that a T cell clone with an invariant Vβ9/Vα4.4 rearrangement proliferated in response to a B cell line transfected with CD1 encoding sequences. The T cell clone also proliferated in response to splenic LPS-activated wild type cells, which response was inhibited by the monoclonal antibody 3C11.

What these experiments show is that certain T cell clones, which are isolated and grown in culture, and which have a specific invariant rearrangement of the T cell receptor, are able to recognize CD1 as a stimulating antigen (for example, see Amano *et al.* page 1714, under the heading "T cell recognition is not associated with β_2m").

In the specific teachings of the primary reference, Amano *et al.* identify two subpopulations of splenic B cells that express high levels of a ß2m-dependent form of CD1. Amano *et al.* go on to suggest that T cell recognition of CD1 on the surface of B cells might play a role in the pathogenesis of systemic lupus. The basis for this assertion is the finding that $CD4^+$ and $CD8^+$ T cells expressing anti-CD1 TCR transgenes obtained from a Vß9/V4.4 T cell clone will induce lupus when transferred into syngeneic BALB/c nude hosts. Amano *et al.* then cite the Zeng *et al.* (1998) paper to support this position[1].

It is important to the understanding of the unexpected results in the present patent application that one understand the cells involved in recognition of CD1. CD1 is not an antigen for conventional T cells, which are restricted to the major histocompatibility antigens by their receptor.

---

1 Reference 33 of Amano *et al.*

However, there is another class of cells, termed NKT cells, termed NK T cells, which are neither typical T cells nor typical NK cells, but which bear an α/β antigen receptor, ands some of the markers typical of NK cells. These cells have a restricted antigen receptor repertoire, predominantly made up of an invariant rearrangement of the Vα14 and Jα281 gene segments, associated with Vβ7 or Vβ8 receptor. This receptor seems to be restricted to interacting with glycolipid antigens presented by the cell-surface molecule, CD1. NKT cells are also apparently limited in their cytokine repertoire.

A major drawback of the work published by Amano *et al.*, and Zeng *et al.*, is the use of a transgenic animal model, which requires transferring disease causing T cells into an immune compromised recipient. In this model, transgenic animals were created which had transgenic T cell receptors that recognized CD1. The transgene is then expressed in a majority of T cells in the animal. But because these coding sequences are artificially introduced, expression is not restricted to the NKT cell population, but rather is found on conventional T cells, which have different properties that NKT cells. The transgenic cells used in this work are (a) artificially found at a very high concentration; (b) artificially expressing a receptor on a different class of cells and (c) artificially transferred into a host animal.

Because of the many artificial features of this model system, one could not draw any conclusions, certainly not conclusions with reasonable certainty, about the role of CD1 in lupus. In particular, the subset of cells that express the transgene is an important point.

Amano *et al.* report a double negative cell line that is **CD4$^-$CD8$^-$**, which expresses the Vβ9/Vα4.4 receptor, and which proliferates in response to CD1. The same T cell receptor, when expressed as a transgene, was associated with single positive cells (**CD4$^+$CD8$^-$** or **CD4$^-$CD8$^+$**) in one transgenic mouse; and with double negative cells (**CD4$^-$CD8$^-$**) in another mouse (see Zeng *et al.* page 526, last paragraph).

The key importance of this is that the injection of the double negative cells, which correspond to the cells that originally expressed the transgene, were **protective of disease**, while the single positive cells, which do not correspond to the original cell type, **caused a disease** phenotype.

Therefore, the data presented by Zeng *et al.* (1998) (and thus cited by Amano *et al.*) demonstrate that animals transgenic for a T cell receptor that recognizes CD1 do not develop disease; and that certain populations of the T cells can be transferred to **cause** disease, while other populations of T cells **suppress** disease. From these findings, one of skill in the art could not conclude with any degree of certainty that CD1 would have a causative effect in lupus.

One of skill in the art would not have reason to believe that the cells tested by Amano *et al.*, which expressed Vβ9/Vα4.4 in a double negative cell, would prevent disease. The only pathological cells were those that artificially expressed the Vβ9/Vα4.4 transgene in a single positive cell, and even then, only after transfer to a secondary animal host, while the primary transgenic animal does not develop disease.

Appellants respectfully submit that the secondary references do not remedy the deficiencies of the primary references. Blumberg *et al.* teaches the expression of CD1 on B cells, monocytes and Langerhans cells, but fails to demonstrate the effectiveness of blocking CD1 to treat lupus-like disease.

Hughes provides background for the use of antibodies as therapeutics, but fails to teach the usefulness of antibodies specific for CD1 in the treatment of lupus-like disease.

Kotzin reviews the pathology of lupus, in particular the clonal expansion of anti-DNA antibody-producing B cells. However Kotzin fails to teach an association of CD1 with the disease, and does not show the effectiveness of blocking CD1 to treat lupus-like disease.

Appellants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references. Prior to the *in vivo* demonstration of efficacy provided herein, there was substantial uncertainty as to the correlation between CD1 and lupus, particularly with respect to causality.

Appellants respectfully submit that the invention of Claim 13 is not made obvious by the cited combination of references. As discussed above, the prior art does not provide a reasonable expectation that administration of CD1 would be effective in treating lupus-like disease. The inclusion of a second therapeutic regimen is not relied upon for patentability, but is merely put forth as a variation on Appellants methods.

Based on the teachings of the prior art, one of ordinary skill in the art would not have a reasonable expectation of success for the presently claimed invention. Withdrawal of the rejection is requested.

RELIEF REQUESTED

Appellants respectfully request that the rejection of 1-2, 6-8, 10, 12 and 13 under 35 U.S.C. 103 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Bozicevic, Field and Francis LLP

Date: Oct. 28, 2004

Pamela J. Sherwood, Ph.D.
Reg. No. 36,677

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APPENDIX

1. A method of treating pathogenic polyclonal B cell activation or class switching in a patient, the method comprising:

administering to said patient an effective dose of a CD1 blocking antibody or fragment thereof, wherein said antibody or fragment thereof binds to CD1, and interferes with T cell recognition of CD1;

wherein said dose is effective to reduce the pathogenic symptoms of said polyclonal B cell activation or class switching.

2. The method according to Claim 1, wherein said pathologic polyclonal B cell activation or class switching results in systemic lupus erythematosus.

6. The method according to Claim 1, wherein said antibody is a monoclonal antibody.

7. The method according to Claim 6, wherein said monoclonal antibody is a human or humanized antibody.

8. The method according to Claim 6, wherein said monoclonal antibody specifically binds to human CD1d.

10. The method according to Claim 6, wherein said antibody comprises a cocktail of monoclonal antibodies that bind to multiple human CD1 isotypes.

12. The method according to Claim 2, wherein said administration is by intravenous injection.

13. A method according to Claim 2, further comprising administering to said patient a second therapeutic agent which is an immunosuppressant, anti-inflammatory, or anti-coagulant agent for the treatment of systemic lupus erythematosus.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,544	04/27/2001	Defu Zeng	STAN 190	3043

24353 7590 10/22/2004

BOZICEVIC, FIELD & FRANCIS LLP
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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 10/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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12/26/04 DOCKETED
Appeal Brief 11/22/04
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PTO-90C (Rev. 10/03)

Notification of Non-Compliance With 37 CFR 1.192(c)	Application No. 09/844,544	Applicant(s) ZENG ET AL.	
	Examiner DiBrino Marianne	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *07 July 2004* is defective for failure to comply with one or more provisions of 37 CFR 1.192(c). See MPEP § 1206.

To avoid dismissal of the appeal, applicant must file IN TRIPLICATE a complete new brief in compliance with 37 CFR 1.192(c) within the longest of any of the following three **TIME PERIODS**: (1) **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer; (2) **TWO MONTHS** from the date of the notice of appeal; or (3) within the period for reply to the action from which this appeal was taken. **EXTENSIONS OF THESE TIME PERIODS MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☐ The brief does not contain the items required under 37 CFR 1.192(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, pending or cancelled, or does not identify the appealed claims (37 CFR 1.192(c)(3)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 1.192(c)(4)).

4. ☐ The brief does not contain a concise explanation of the claimed invention, referring to the specification by page and line number and to the drawing, if any, by reference characters (37 CFR 1.192(c)(5)).

5. ☐ The brief does not contain a concise statement of the issues presented for review (37 CFR 1.192(c)(6)).

6. ☐ A single ground of rejection has been applied to two or more claims in this application, and

   (a) ☐ the brief omits the statement required by 37 CFR 1.192(c)(7) that one or more claims do not stand or fall together, yet presents arguments in support thereof in the argument section of the brief.

   (b) ☐ the brief includes the statement required by 37 CFR 1.192(c)(7) that one or more claims do not stand or fall together, yet does not present arguments in support thereof in the argument section of the brief.

7. ☒ The brief does not present an argument under a separate heading for each issue on appeal (37 CFR 1.192(c)(8)).

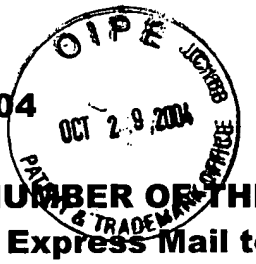
8. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 1.192(c)(9)).

9. ☒ Other (including any explanation in support of the above items):

Under Status of Claims, the following items need to be corrected or added: restriction requirement was mailed October 25, 2002. Claim 11 was canceled in Applicant's response of December 19, 2003. Under Issue on Appeal section, claims 1, 2, 4-8, 10 and 12 are listed as rejected under 103(a) as unpatentable over Amano et al in view of Kotzin et al, Zeng et al, Blumberg et al and Hughes, however, claims 4 and 5 were canceled and are not presently under rejection.

Christina Chan
CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Marianne DiBrino 10/18/04



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Signature Stuart McLeish Date 10/28/04

Atty. Docket No.	Serial Number	Description	Atty.	Fee
STAN-190	09/844,544	Transmittal, Appeal Brief *in triplicate*, Copy of Notice of Non-Compliant Appeal	PJS	
BEAR-004	09/642,609	IDS w/Fee Authorization *in duplicate,* Copy of EP Communication dated 07/28/04, (1) Cited Reference	PAB	$180
UCAL-170CON7	10/099,379	Transmittal, Fee Sheet *in duplicate,* Amendment w/Petition for a 2 Month Extension of Time, IDS, SB08A, Courtesy Copy of 101 Previously Cited References	PAB	$235
SNDR-001CIP (SNDR-001)	09/307,956 09/132,021	Revocation of POA/Change of Address	CLF	
RIGL-004CON4	09/919,635	Transmittal, Response to Notice of Non-Compliant Amendment, Amendment, Exhibit a, Declaration, Copy of Office Communication	JSK	